specification at page 5, last paragraph, page 6, last paragraph, page 7, first paragraph, page 28, last paragraph, page 30, second full paragraph, and page 33, third paragraph.

It is noted that the Examiner did not review the Information Disclosure Statement submitted on July 24, 1995. It is assumed that this was because this paper had not yet been placed in the file at the time the Examiner completed the first Office Action. The Examiner is requested to review the Information Disclosure Statement and the references cited therein before issuing a second Action on the merits. If the paper has not yet been matched to the file, the Examiner is requested to call the undersigned at which time a copy of the IDS and Form PTO-1449 and filing receipt if required will be promptly forwarded.

In the Official Action from the Examiner mailed August 6, 1996, claims 23, 24 and 35 were provisionally rejected under 35 U.S.C. 101 as claiming the same invention as claims 53, 54 and 56 of copending U.S. application 08/302,241. Since claims 23 and 24 are now canceled, it is respectfully submitted that this provisional rejection is no longer applicable to these claims. Claim 35 has been amended as set forth above. However, applicants are willing to cancel the corresponding claim 56 from copending application 08/302,241 upon receiving a Notice of Allowability for the instant

claims. Therefore, it is respectfully requested that this provisional rejection as it applies to claim 35 be deferred until allowable subject matter is indicated.

Claims 1-11, 14-22, 25-28, and 36-38 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 51-63 of co-pending application Serial No. 08/302,241. The Examiner asserts that though the conflicting claims are not identical, he is of the opinion that they are not patentably distinct from each other because the recombinant DNA containing the complete sequence of a GS gene, vectors containing said GS gene and methods for co-amplifying genes of interest recited in co-pending application (08/302,241), differ only slightly in scope from those recited in the above-identified application, or differ in the physical description of the subject matter. The Examiner further states that since the GS gene is amplifiable, it must be considered that the two sets of claims are not patentably distinct. While not agreeing with this provisional rejection, applicants respectfully submit that in view of cancellation of the above claims, this rejection is now moot and should therefore be withdrawn. Applicants have canceled these claims without prejudice to further prosecution in related applications.

Claims 1-34 and 36-38 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 5,122,464 (the '464 patent). The Examiner asserts that although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed recombinant DNAs encoding GS genes, expression vectors containing said genes, methods for co-amplifying a non-GS gene, use of the GS gene as a dominant selectable marker, etc. differ only in scope and encompass overlapping subject matter. While not agreeing with this rejection, applicants submit that in view of the cancellation of claims 1-34 and 36-38, this rejection is now moot. In addition, although the subject matter of claims 12 and 13 has been incorporated into new claims 39-42 to place them in better condition for examination, it is respectfully submitted that application of a double patenting rejection to claims 12 and 13 or to claimed subject matter derived therefrom is improper. Claims drawn to probes and methods of hybridization were originally separated from claims drawn to DNA sequences, vectors and use of the vectors as selectable markers in the restriction requirement set forth in Paper No. 4 of copending Application Serial No. 08/302,241. It is not proper to hold claims 12 and 13 as being obvious over the patented claims when the

claimed subject matter was previously restricted. Thus, applicants respectfully request that this rejection be withdrawn and not be applied to new claims 39-42, also drawn to hybridization methods.

Claims 8, 12 and 13 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to adequately teach how to make and/or use, and/or allegedly fails to provide a written description of the invention as claimed. The Examiner argues on page 4 of the Office Action that applicants claim a recombinant DNA from any species which hybridizes under high stringency conditions to a DNA encoding a GS protein without presenting any teachings on how this DNA is to be obtained or what is meant by "high stringency" hybridization conditions. Furthermore, the Examiner alleges that while applicants claim the use of a GS gene as a hybridization probe, they have not recited the conditions under which the probe is prepared, the conditions under which the DNA is used as a probe, the target to be identified, etc. Also, the Examiner argues that while applicants claim use of a GS gene as a diagnostic probe for the detection of disease conditions, applicants present no teachings on how the skilled artisan would prepare and use the GS gene as a diagnostic probe for such a detection process. The Examiner also states that applicants have not

cited any relevant portions of prior art documents to provide guidance for the skilled artisan to practice the claimed invention.

Applicants respectfully traverse. The Examiner is incorrect in the statement that no relevant prior art documents were submitted to provide guidance for hybridization methods and conditions. In the IDS filed July 24, 1995, applicants submitted pages from a section of the Molecular Cloning manual of Maniatis et al. entitled "Hybridization of DNA or RNA Immobilized on Filters to Radioactive Probes" (please see reference AN1).

Furthermore, it is well established that "[A] patent need not teach, and preferably omits, what is well known in the art" (**Hybridtech Inc. v. Monoclonal Antibodies, Inc.**, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986)). The use of hybridization probes produced from isolated genes is extremely well known in the art, as are methods of modifying hybridization conditions and stringency to detect different nucleic acid populations. See for example the attachment included in Exhibit A taken from Benjamin Lewin's Genes IV (Oxford University Press, 1990) where it is stated:

> The ability of related but not identical complementary sequences to recognize each other can be controlled by the **stringency** of the conditions imposed for the reassociation. A higher stringency is imposed by (for example) an increase in temperature, which requires a greater degree of

> complementarity to allow base pairing. So by performing the hybridization reaction at high temperatures, reassociation may be restricted to rather closely related members of a family; at lower temperatures, more distantly related members may anneal.

In view of this passage which exemplifies the well-known procedure of adjusting hybridization stringency depending on the target nucleic acid, it would be obvious to the skilled artisan that standard hybridization conditions well known in the art as given in the previously submitted passage from Maniatis et al. are routinely modified without undue experimentation to accomplish different objectives.

Applicants' objectives include methods of using the disclosed GS-specific nucleic acids as hybridization probes. The purposes of such methods have been clearly established in the specification at the bottom of page 6 and top of page 7, where it is stated that the disclosed DNA sequences or fragments thereof may be used as hybridization probes for obtaining GS coding sequences from other species, or for detecting disease states in which the level of GS in a subject is altered.

Applicants have clearly demonstrated in the specification by describing several Southern hybridization experiments analyzing the presence or amplification of GS-specific sequences that differences in nucleic acid levels in a particular cell may be easily quantified by comparing the

level of probe signal to a standard control (see for example page 28, last paragraph). With this fact in hand, it should be a routine task for the skilled artisan to perform a diagnostic assay using the GS probe in order to quantitate a difference in or absence of GS expression, using standard techniques known in the art.

Thus, applicants respectfully submit that the rejection of claims 8, 12 and 13 was improper. Although these claims have now been canceled and replaced by claims 39-42, applicants request that the rejection under 35 U.S.C. 112, first paragraph, not be applied to the new claims for the same reasons as set forth above.

Claims 8, 12-13, 15, 17-19 and 26-38 have been rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

While not necessarily agreeing with the Examiner's position, we submit that in view of the cancellation of claims 8, 15, 17-19, 26-34 and 36-38, the rejection as applied to these claims is now moot and should therefore be withdrawn.

The Examiner argues that while claims 12 and 13 provide for the use of the GS gene, since the claim does not set forth any steps involved in the method/process, it is unclear

what method/process Applicants are intending to encompass. The Examiner also argues that a claim is indefinite when it does not describe any active, positive steps. In addition, the Examiner rejects claims 12 and 13 under 35 U.S.C. 101 because the claimed recitation of a use results in the improper definition of a process. Finally, claim 13 is also rejected for being a substantial duplicate of the recombinant DNA claimed in claim 1 (now canceled) since intended use bears no patentable weight.

The subject matter of claims 12 and 13 has now been incorporated into newly written claims 39 and 40. Since the newly written claims address all concerns expressed in the rejection of claims 12 and 13 under both 35 U.S.C. 112, second paragraph and 35 U.S.C. 101, these rejections should not be applied to newly submitted claims 39 and 40.

The Examiner argues that claim 35 also recites an intended use of the claimed vector, and that the intended use of a compound or composition carries no patentable weight and is not proper claim language. Applicants respectfully submit that claim 35 as amended does not recite an intended use. Accordingly, this rejection should now be withdrawn.

In view of the foregoing amendments and remarks, it is requested that the rejections of record be reconsidered and withdrawn, and that the application be found to be in allow-

able condition. If a personal conference would in any way help to advance the prosecution of this application, the Examiner is requested to telephone the undersigned.

No additional fee is believed to be necessary. However, the Commissioner is hereby authorized to charge any additional fees which may be required for this amendment, or credit any overpayment to Deposit Account No. 19-3700 and to notify the undersigned.

Respectfully submitted,

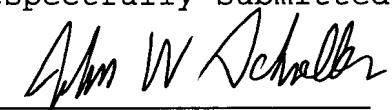

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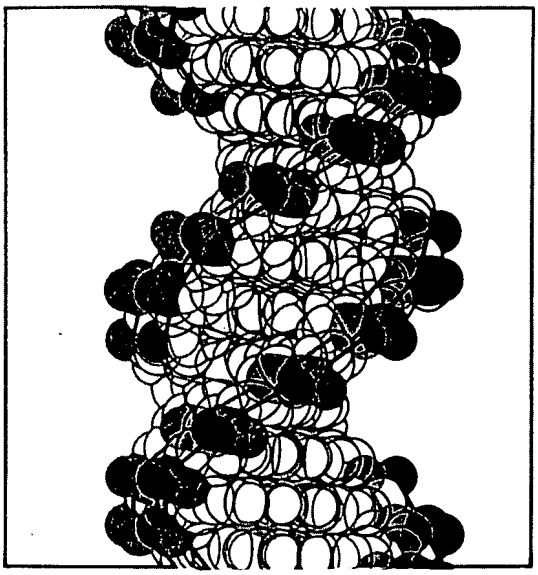
Exhibit A



GENES IV

BENJAMIN LEWIN

1990
Oxford University Press
Oxford New York Tokyo Melbourne
Cell Press, Cambridge

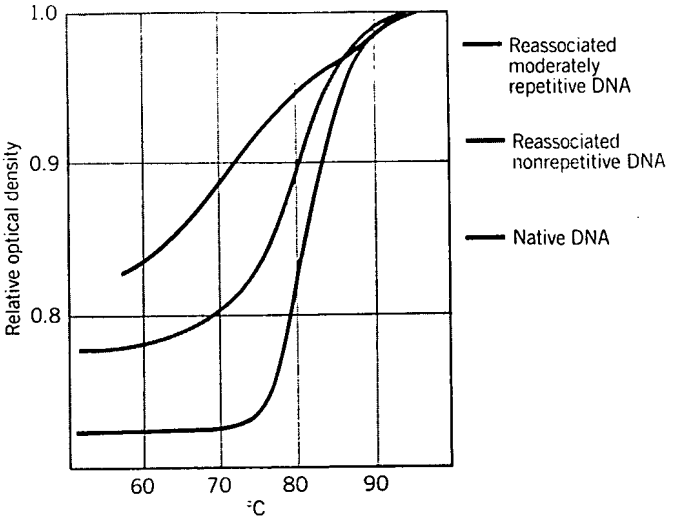


Figure 24.7
The denaturation of reassociated nonrepetitive DNA takes place over a narrow temperature range close to that of native DNA, but reassociated repetitive DNA melts over a wide temperature range.

in **Figure 24.7.** This means that they do not consist of exactly paired molecules. Instead, they must contain appreciable mispairing. The more mispairing in a particular molecule, the fewer hydrogen bonds need be broken to melt it, and thus the lower the T_m.

The breadth of the melting curve shows that renatured repetitive DNA contains a spectrum of sequences, ranging from those that have been formed by reassociation between sequences that are only partially complementary, to those formed by reassociation between sequences that are very nearly or even exactly complementary. How can this happen?

Repetitive DNA components consist of families of sequences that are not exactly the same, but are related. The members of each family consist of a set of nucleotide sequences that are sufficiently similar to renature with one another. The differences between the individual members are the result of base substitutions, insertions, and deletions, all creating points within the related sequences at which the complementary strands cannot base pair. The proportion of these changes establishes the relationship between any two sequences. When two closely related members of the family renature, they form a duplex with high T_m; when two more distantly related members associate, they form a duplex with a lower T_m.

The ability of related but not identical complementary sequences to recognize each other can be controlled by the **stringency** of the conditions imposed for reassociation. A higher stringency is imposed by (for example) an increase in temperature, which requires a greater degree of complementarity to allow base pairing. So by performing the hybridization reaction at high temperatures, reassociation may be restricted to rather closely related members of a family; at lower temperatures, more distantly related members may anneal. Note also that, as the stringency of hybridization increases, the proportion of the genome in the nonrepetitive fraction also increases.

There is wide variety in the construction of repetitive families. Some families are well-defined, and consist of quite closely related members. They remain intact even when the stringency of hybridization is increased. Other families consist of a continuum of variously related sequences, so that their apparent membership declines continuously as the stringency is increased. The measured size of such repetitive families is arbitrary, since it is determined by the hybridization conditions.

The reassociation of two sequences that are related but not identical occurs more slowly than the reaction between identical sequences. Because a greater Cot is required for the reassociation of related sequences, the $Cot_{1/2}$ values observed for repetitive fractions may be higher than really corresponds to the complexity.

Repetitive components therefore often have lower complexities and greater repetition frequencies than implied by their reassociation kinetics. For example, related sequences with a repetition frequency of 3–4 are likely to have a $Cot_{1/2}$ that places them in the nonrepetitive fraction.

As a result of this effect, related sequences occur in the "nonrepetitive" fraction as well as in the avowedly repetitive DNA. Such sequences now are most commonly identified by performing Southern blotting at reduced stringency. At high stringency, a probe to nonrepetitive DNA may react with only a single genomic sequence. As the stringency is reduced, it may react with additional, related sequences.

What is the origin of related sequences in nonrepetitive DNA? Probably at one time there was a single sequence; then it become duplicated, after which changes in the sequences of one or both copies led to their divergence into related sequences. The extent of such relationships varies enormously within a eukaryotic genome, from sequences that are virtually identical (and reside in repetitive DNA) to those whose relationship is barely detectable (and which are to all intents and purposes nonrepetitive).

Most Structural Genes Lie in Nonrepetitive DNA

Mendelian genetics for simple traits imply that there is only one copy of each determining factor in the haploid genome. The factor can be mapped to a particular locus; and the simplest assumption is that each such locus is occupied by a DNA sequence representing a single protein, as exemplified by the definition of the gene in Chapter 3.